OTA HIGHLIGHT PAPER

Negative Pressure Wound Therapy Reduces the Effectiveness of Traditional Local Antibiotic Depot in a Large Complex Musculoskeletal Wound Animal Model

Daniel J. Stinner, MD, Joseph R. Hsu, MD,† and Joseph C. Wenke, PhD‡*

Objectives: Negative pressure wound therapy (NPWT) has been used to help manage open wounds. Surgeons also often use local antibiotic depot as adjunctive therapy in an effort to reduce infection rates. These 2 techniques have been reported to be used in conjunction, but there are little data to support this practice. We sought to compare the contamination levels of wounds treated with the commonly used antibiotic bead pouch technique to wounds that received both antibiotic beads and NWPT.

Methods: The effectiveness of a bead pouch was compared with antibiotic beads with NPWT. The anterior compartment and proximal tibia of goats were injured and inoculated with *Staphylococcus aureus*. Six hours later, the wounds were debrided and the animals were assigned to a group; the bacteria level was quantified immediately before and after initial debride ment and 2 days after treatment.

Results: The wounds in the antibiotic bead pouch group had 6 fold less bacteria than the augmented NPWT group, 11 ± 2% versus 67 ± 11% of baseline values, respectively (P 0.01). As expected, high levels of the antibiotic were consistently recovered from the aug mented NPWT effluent samples at all time points.

Conclusions: NPWT reduces the effectiveness of local antibiotic depot. These results can provide surgeons with the information to personalize the adjunctive therapies to individual patients, with the degree of difficulty in managing the wound and concern for infection being the 2 variables dictating treatment.

Key Words: Negative pressure wound therapy, local antibiotics, bead pouch, orthopaedic infection

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From the *Department of Regenerative Medicine, United States Army Institute of Surgical Research; †Department of Orthopaedics and Rehabilitation, Brooke Army Medical Center; and ‡Department of Regenerative Medicine, United States Army Institute of Surgical Research, Fort Sam Houston, TX.

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Reprints: Daniel J. Stinner, MD, United States Army Institute of Surgical Research, 3400 Rawley E. Chambers Avenue, Fort Sam Houston, TX 78234 (e-mail: daniel.stinner@gmail.com).

INTRODUCTION

Despite the many advances in healthcare, open fracture management continues to pose a challenge for the treating surgeon. Severe lower extremity trauma can be fraught with complications, with infection being one of the most common.[1] Infection is often responsible for rehospitalization,[1,2] which is a predictor of poorer clinical outcomes.[3] The high infection rate seen with severe lower extremity trauma, up to 50% in some series, highlights the fact that the current standard of care, including intravenous antibiotics and early debridement and irrigation, leaves room for improvement.[4] As a result, several adjunctive treatments have gained popularity, in particular, local antibiotic delivery via polymethylmethacrylate (PMMA) bone cement and negative pressure wound therapy (NPWT).

In cases with gross contamination, established osteomyelitis, or those with significant soft tissue and bone injuries requiring dead space management, local antibiotic delivery using PMMA beads presents an attractive option. Antibiotic-impregnated PMMA beads can provide extremely high doses of antibiotic locally while systemic levels remain low. This high level within the wound is effective against biofilm-based bacteria and reduces the potential systemic toxicity associated with parenteral administration.[5,6] In addition, when using the antibiotic bead pouch technique, the semipermeable barrier protects the wound from secondary contamination.

Another frequently used option for the treatment of open wounds is NPWT. Initially developed over a decade ago for the treatment of chronic nonhealing wounds,[7] its application has spread rapidly to include the treatment of acute contaminated open wounds, among others.[8] It has been proven to be an effective way to manage large complex injuries to soft tissue and has been shown to reduce infection rates in severe open fractures when compared with standard dressings.[9] However, more recent data suggest that NPWT is not as effective in minimizing gram-positive bacteria, such as *Staphylococcus aureus*, in contaminated wounds.[10,11]

Although little is mentioned in orthopaedic literature, some interest has developed in "combination therapy," where NPWT is used in conjunction with antibiotic-impregnated PMMA beads.[12–15] The combination of these 2 techniques may improve outcomes because of the benefits of better soft tissue management, by NPWT, and increased local antibiotic levels, by the implanted PMMA beads. Furthermore, there is a possibility that the combination will mitigate the difficulties of the individual techniques, such as proximity of NPWT to neurovascular structures,[16] maintaining the seal of the bead

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pouch alone, and concerns of bacterial overgrowth in the cases of NPWT failures because of the loss of suction[17] (Figs. 1, 2).

On the contrary, there is a possibility that with this augmented NPWT technique, the antibiotics that are eluted out from the antibiotic PMMA beads will not diffuse from the depot and permeate throughout the wound, but rather will be removed from the wound via the negative pressure device. This study tests our hypothesis: NPWT will reduce the effectiveness of antibiotic beads. We used a large animal-contaminated defect to compare the contamination levels of wounds treated with the commonly used antibiotic bead pouch (ABP) technique to wounds that received augmented NPWT (both antibiotic beads and NWPT).

MATERIALS AND METHODS

PMMA Bead Manufacture and Elution Testing

The PMMA beads were made in an aseptic manner using acrylic bone cement (Surgical Simplex P; Stryker, Mahwah, NJ). Number-5 Ethibond (Ethicon, Inc, Somerville, NJ) was routed into the grooves of a 7-mm bead mold. Powdered cement (40.0 g) was then mixed with 2 g of vancomycin and 20 mL of liquid monomer. Vancomycin was chosen as the local antibiotic because *S. aureus*, which is the bacterium used in this study, is sensitive to the drug. Vancomycin is also available in a powder form and is heat stable. The resulting paste was then evenly pressed into the bead mold, filling all holes with the cement mixture. The top portion of the bead mold was pressed firmly over the cement-filled mold. After the cement began to harden, the strand of antibiotic beads was removed from the mold and excess cement was trimmed from the edges. The antibiotic beads, 8 beads per strand, were then weighed and stored in a sealed sterile specimen cup until use.[18] These bead strands were used in both groups.

The antibiotic elution was also determined for the antibiotic beads used in this study. Four vancomycin-loaded antibiotic beads were weighed, placed into separate containers of 10 mL of phosphate-buffered solution (PBS) with a pH of 7.4, and put on a shaker incubator at 37°C. Measurements were taken at 1, 3, 7, 14, and 21 days. At each time point measured, the antibiotic beads were removed, washed with 1 mL of PBS, weighed, placed into a new container of 10 mL of PBS, and put back on the shaker incubator at 37°C. Aliquots measuring 1 mL were then taken from the resultant elutions at each time point measured. The vancomycin concentration of each aliquot was then determined.

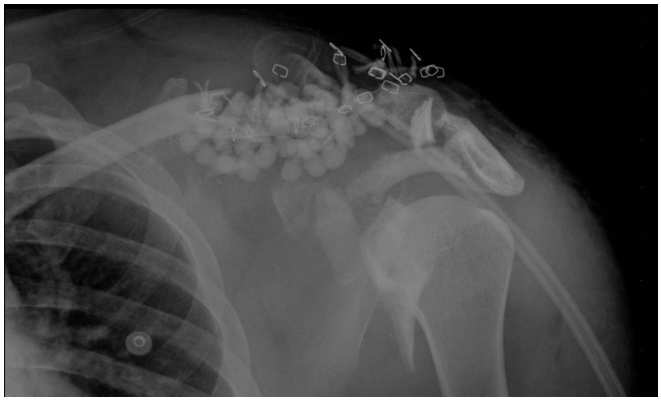

FIGURE 1. The antibiotic-impregnated PMMA beads were effectively used as a barrier to between the neurovascular bundle and the NPWT dressing in this patient who sustained an unexploded rocket propelled grenade injury to his left upper extremity.

Animal Procedures

This study was conducted in compliance with the Animal Welfare Act, the Implementing Animal Welfare Regulations, and in accordance with the principles of the Guide for the Care and Use of Laboratory Animals. All procedures were performed in a laboratory accredited by the Association for Assessment and Accreditation of Laboratory Animal Care following protocol approval from our Institutional Animal Care and Use Committee.

Wound Creation

All animals were fasted before surgical procedures. The 21 castrated, adult male Boer goats (*Capra hircus*) were sedated with ketamine/midazolam and intubated. Anesthesia was maintained with isoflurane and supplemental oxygen. An epidural injection of morphine (0.1 mg/kg) diluted in 0.9% sterile saline solution to a volume of 0.13 mL/kg was given both as an adjunct to general anesthesia and for its durable postoperative analgesic effect. After adequate anesthesia using both general anesthetic and epidural injection, a complex contaminated musculoskeletal wound was created on the hindlimb. As previously described,[11] a 35 cm^2 trapezoidal portion of the skin and fascia covering the anterior tibia was removed. After the anterior tibia and musculature was exposed, a portion of the periosteum was removed, leaving behind a 6-mm strip laterally. A 10-mm cortical defect was created in the metaphyseal region of the proximal tibia using a core reamer. Approximately 13 g of muscle was then removed from the tibialis anterior with bovie electrocautery to maintain hemostasis and a freeze injury was performed to a portion of the remaining muscle by applying a 1 cm × 4 cm metal bar, cooled in liquid nitrogen, for 2 iterations of 30 seconds. Finally, a thermal injury was performed to all exposed muscle, fascia, and periosteum with bovie electrocautery; thus rendering a complex musculoskeletal wound.

This technique resulted in a reproducible complex musculoskeletal wound intended to mimic an open fracture without the need for skeletal stabilization. After creation of the wound, the wound was contaminated with 1 mL of $>2.40 \times 10^8 \pm 1.02 \times 10^8$ colony-forming units per milliliter *S. aureus* (Xenogen 29; Caliper Life Science, Hopkinton, MA), which was spread evenly over the wound surface. These bacteria are genetically engineered to emit photons, allowing for quantification with a photon counting camera system.

After surgery, the wounds were bandaged with Kerlix (Kendall, Mansfield, MA) and Vetwrap dressings (3M Animal Care Products, St Paul, MN), and the goats were recovered in their pens and allowed activity ad libitum for 6 hours. The

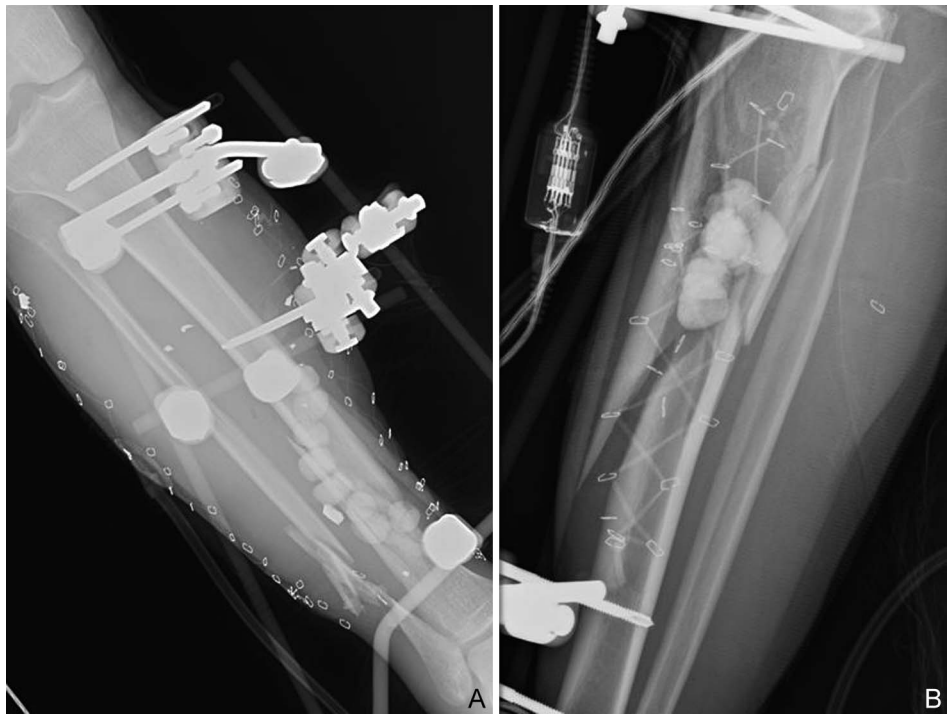

FIGURE 2. Patients in (A) and (B) sustained open tibia fractures in the combat environment and underwent subsequent 4 compartment fasciotomies and external fixation. Before air evacuation to a higher level of care, antibiotic-impregnated PMMA beads were placed under the NPWT dressing because of concern for in-flight NPWT failure or loss of suction. Should loss of suction occur using the combined therapy, the dressing would be converted to a traditional ABP.

goats were re-anesthetized and placed supine on an operating table in a custom light-free imaging chamber. As described previously,[19] a photon counting camera (Charge Couple Device Imaging System Model C2400; Hamamatsu Photonics, Inc, Hamamatsu City, Japan) was used to capture the quantitative and spatial distribution of the live bacteria within the wound. After collection of baseline luminescent data, standard debridement and irrigation was performed with 9 L of normal saline using gravity flow low-pressure irrigation. The imaging sequence was then repeated to obtain postdebridement and irrigation data.

Both groups had 2 strands of 8 antibiotic-impregnated PMMA beads (approximately 258 mg of vancomycin) placed within the wound bed. Goats were then assigned to 1 of the 2 different groups: a control group receiving an antibiotic bead pouch and an experimental group with vancomycin-impregnated PMMA beads and NPWT (ABP and augmented NPWT groups, respectively). The wounds in the ABP group were sealed with a semipermeable membrane; the augmented NPWT received a standard NPWT dressing. The goats were returned to their pens and were allowed water, food, and activity ad libitum. The augmented NPWT group had the device suspended 5 feet above the floor to prevent the animals from tampering with it. The animals were euthanized at 48 hours after injury, and the live bacteria within the wound were quantified using the imaging procedures previously described.

NPWT Effluent Analysis

The effluent solidifying agent, sodium polyacrylate (DeRoyal Industries, Powell, TN), was removed from the NPWT canister before the study to prevent interference with effluent sampling. Samples of the NPWT effluent from the experimental group were obtained at 6, 12, 24, 36, and 42 hours after treatment initiation. Effluent analysis was performed to determine the amount of vancomycin present in the sample using reversed phase high-performance liquid chromatography (Charles River Laboratories, Shrewsbury, MA).[20]

Data Analysis

Gray-scale images were first obtained. The bacterial luminescent picture was then superimposed on the gray-scale image. This allowed for both the location and intensity, in terms of photon number, of the bacteria to be quantified within the wound. Photon counts at each time point were normalized by the baseline photon counts (6 hours before debridement and irrigation). All data were analyzed using 1-way analysis of variance with repeated measures using SAS statistical software (SAS Institute, Cary, NC) with significance set at $P < 0.05$.

RESULTS

In Vitro Antibiotic Elution

Antibiotic elution measurements demonstrated an initial burst of antibiotic release in the first 24 hours (37.8 ± 1.5 μg/mL), followed by a rapid decline at 3 days (4.0 ± 0.2 μg/mL). There was a steady decline in elution concentration out to 21 days (Fig. 3).

Quantitative Analysis

The baseline photon count before the debridement and irrigation were similar between the 2 groups (ABP = $6.89 \times 10^5 \pm 1.17 \times 10^4$, augmented NPWT = $4.99 \times 10^5 \pm 7.93 \times 10^4$). The debridement and irrigation reduced the bacteria levels in the

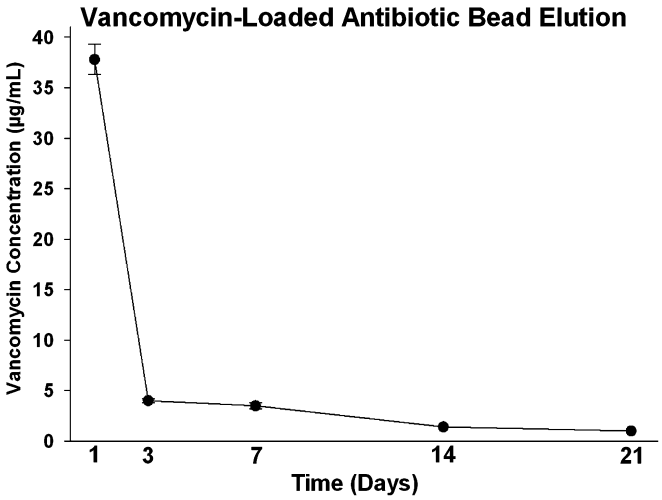

FIGURE 3. The graph highlights the initial high release of antibiotic from the antibiotic-impregnated PMMA bead. Although the amount of antibiotic eluted quickly decreases, it continues to elute out from the bead over the entire period evaluated (21 days).

wounds of the ABP and augmented NPWT groups a similar amount (29 ± 2% and 30 ± 4% of baseline values, respectively; $P = 0.92$). The ABP resulted in much less bacteria within the wounds than the augmented NPWT, 11 ± 2% versus 67 ± 11% of baseline values, respectively ($P = 0.01$; Fig. 4).

Spatial Distribution of Bacteria Within the Wound

Analysis of the spatial distribution of the bacteria revealed that the wounds in the 2 groups had similar spatial distribution within the wound before receiving treatment (Figs. 5A, 6A). After treatment, the wounds that received the ABP technique had very few bacteria (Fig. 5B). The bacteria were generally found just along the edge of the wounds and primarily at the proximal and lateral aspect of the wounds. However, in the wounds treated with augmented NPWT, the bacteria were present in the entire wound (Fig. 6B). Closer examination of the black and white photographs with the beads in place (Fig. 7A) and removed (Fig. 7B) demonstrate that the bacteria grew up to the footprint of the antibiotic beads in most cases, but were often not present in the tissue in direct contact with the antibiotic beads.

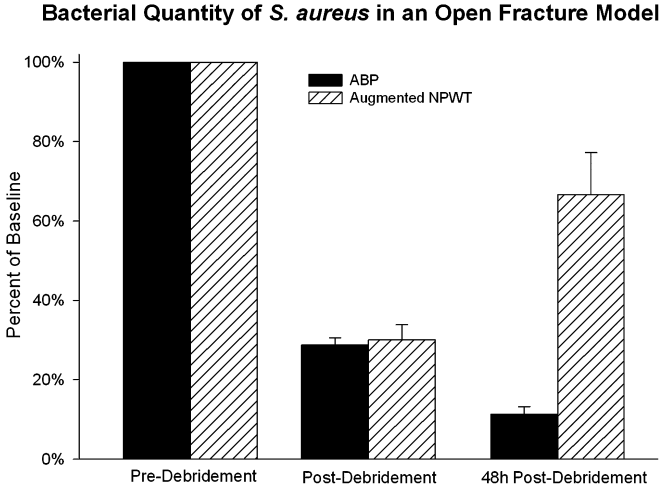

FIGURE 4. Bacterial quantity in wound compared with baseline levels. Comparison of the percentage of *Staphylococcus aureus* remaining in the wound at various time points.

Antibiotic Effluent Levels

High levels of antibiotic were consistently recovered from the augmented NPWT effluent samples at all time points (51 ± 3 µg/mL). The lowest level was 6 hours after implantation and peaked at 12 hours, which measured 42 and 64 µg/mL, respectively.

DISCUSSION

As a result of infection being a relatively common and potentially devastating consequence in severe musculoskeletal trauma, multiple adjunctive treatments to minimize the risk of infection are being used in the treatment of these injuries to include NPWT and local antibiotic delivery. In this study, an established large animal musculoskeletal wound model[11] was used to compare the effectiveness of a commonly used local antibiotic delivery technique to a newly described technique, using antibiotic-impregnated PMMA beads with NPWT (augmented NPWT).[12] As suspected, the NPWT reduced the effectiveness by removing the antibiotics from the wound.

NPWT was initially developed for the treatment of chronic nonhealing wounds and has demonstrated significant benefits in wound healing, which is achieved by increasing blood flow and granulation tissue.[21] Indications for its use have widely expanded because of its successful application in the management of open fractures,[9,22] high-risk surgical incisions,[23] draining hematomas,[24] and the treatment of exposed tendon, bone, and hardware,[25] among others. In addition, various techniques are published describing augments to NPWT to further increase its effectiveness, such as the addition of a deep drain to decrease dead space without delaying wound closure[26] the addition of silver to the NPWT dressing,[27] and, as tested in the current study, the addition of local antibiotics via antibiotic-impregnated PMMA beads.[12]

Previous work[11] performed by the same surgeon, using the same animal model and methods with wounds contaminated with *S. aureus* (lux), demonstrated much higher bacterial rebound at 48 hours using standard NPWT when compared with the current study groups. Despite the reduced effectiveness seen in wounds treated with augmented NPWT in the current study, this technique may prove better than NPWT alone. It also seems to be a more effective adjuvant than silver dressings.[11] One of the benefits of the antibiotic-impregnated PMMA beads is the initial high levels of antibiotic elution into the surrounding wound bed within the first 24–48 hours. The antibiotic elution levels typically taper off relatively quickly while still continuing to elute smaller amounts of antibiotic over time as demonstrated in the current study.[28–30] The release kinetics from beads provide high initial

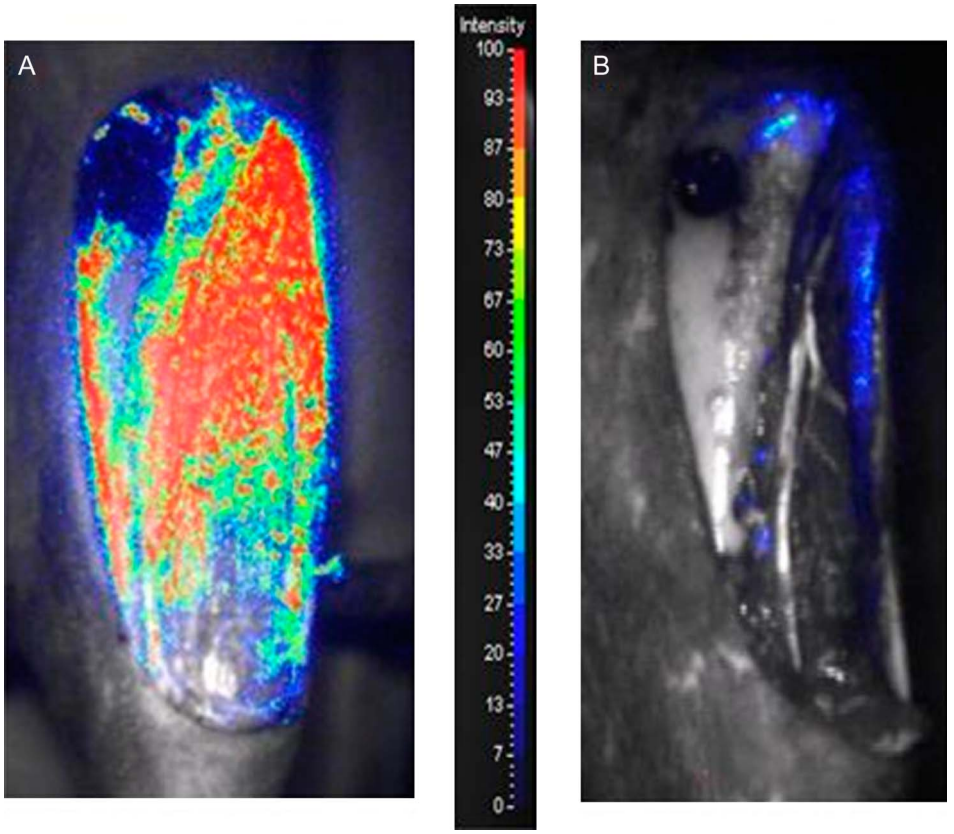

FIGURE 5. Spatial distribution and relative levels of bacteria within the wound at baseline level (A) and after ABP therapy for 2 days (B).

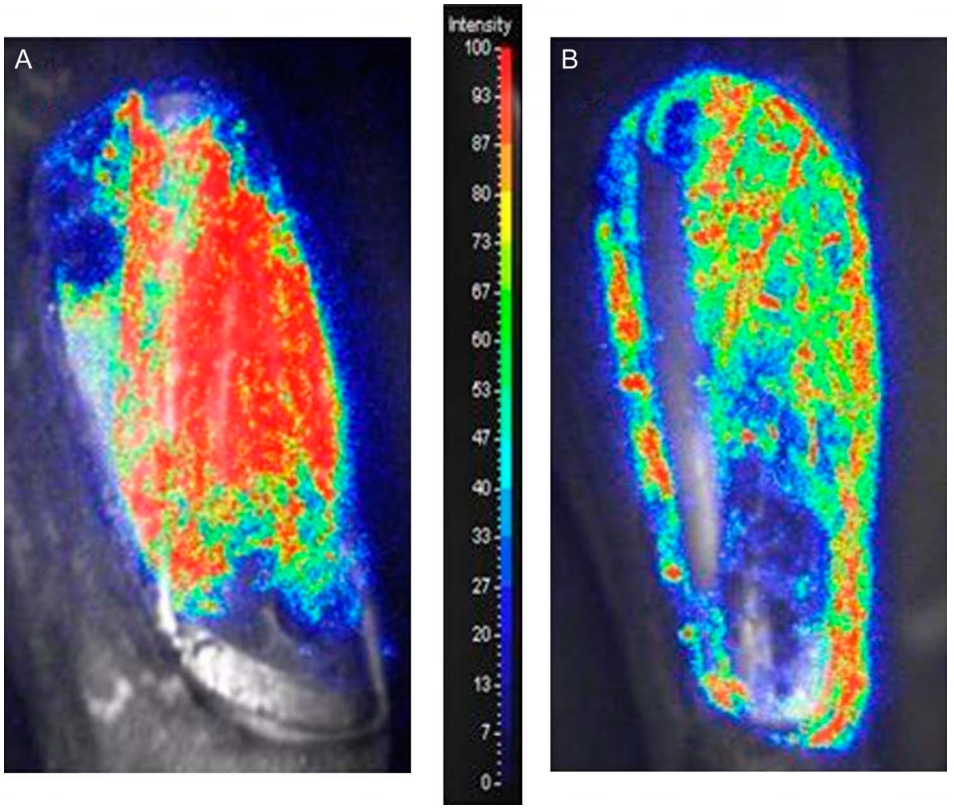

FIGURE 6. Spatial distribution and relative levels of bacteria within the wound at baseline level (A) and after augmented NPWT for 2 days (B).

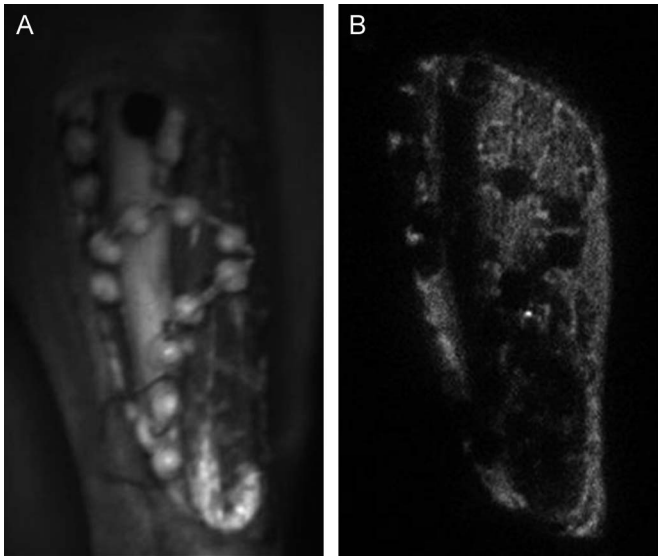

FIGURE 7. Black and white photograph demonstrating bead placement (A). Black and white photograph demonstrating bacteria growing up to the footprint of the beads in the augmented NPWT group (B).

levels of antibiotics, which are often required to kill bacteria that are within a biofilm, and generally provides antibiotic levels over the minimum inhibitory concentration (MIC) for up to 2 or 3 weeks. For use in a bead pouch or augmented NPWT, the elution properties are adequate because the dressing is often changed every 2–3 days, and the beads are often discarded or exchanged. If bacterial reduction is the primary goal, the standard ABP is the most effective, as demonstrated in the current study; however, controlling or preventing infection is multifactorial to include optimizing the local biology. On the contrary, if NPWT is used alone, the benefits of wound healing will likely be achieved, but it will not have as significant an impact on bacterial reduction in the wound. Augmented NPWT, although not as effective in reducing gram-positive bacteria as the standard ABP, seems to be more effective than NPWT used alone.

As with all preclinical research, this study has several limitations. First, we used an animal model; however, the goat tibia's relative size and subcutaneous nature allow for relevant preclinical in vivo testing of clinician-dependent interventions in a contaminated complex musculoskeletal wound model. Second, although commonly used in the clinical setting, systemic antibiotics were not used in this study to minimize confounding variables and allow independent assessment of the interventions being tested.

In summary, NPWT reduces the effectiveness of local antibiotic depot. However, if NPWT is indicated and there is concern about bacterial contamination within the wound, the addition of antibiotic beads may be beneficial, albeit on a more limited scale than the traditional local antibiotic depot. Future work should focus on developing local antibiotic delivery systems and a method of using NPWT that can be more effectively used in combination to maximize the individual benefits each treatment offers when used in isolation. Local antibiotic depot relies on elution of the drug from the carrier and to diffuse across the wound to contact the bacteria. NPWT seems to remove the antibiotic from the wound before it can come into contact with the bacteria, particularly the bacteria that are further away from the antibiotic beads.

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